g) selecting a transgenic mouse homozygous for the mutant GP IIIa (β_3) gene from the resulting progeny.

h) (New) A method of determining the effect of an agent on a biological response of the transgenic mouse of claim 1, wherein the biological response is mediated by GP IIIa (β_3) phosphorylation, the method comprising:

a. administering the agent to the mouse;

b. determining the effect of the agent on the biological response.--

REMARKS

Responsive to the Office Action dated July 29, 2002 (Paper No. 13), Applicants respectfully request reexamination and reconsideration of the above-identified application in view of amendments and remarks made herein.

Applicants are filing this Amendment and Response together with a Request for Continued Examination and a Request for a Three-Month Extension of Time.

In this Amendment and Response, Applicants have cancelled claims 1-68 without prejudice or disclaimer and added new claims 69-92. New claims 69-92 will, therefore, be pending after entry of this Amendment and Response. Support for the newly added claims lies in the specification and original claims as filed. No new matter has been added by virtue of the amendments contained herein.

In addition, Applicants have amended the title to more accurately reflect what is presently being claimed.

OBJECTION TO THE SPECIFICATION:

The Specification is objected to under 35 U.S.C. §132, because the Examiner alleges that the Amendment and Reply under 37 C.F.R. §1.111 filed on January 2, 2002 (Paper No. 6), introduces new matter into the disclosure. Applicants respectfully disagree with the Examiner, but in order to expedite prosecution, Applicants have amended the specification to delete the subject matter added to the specification in Applicants' Amendment and Reply under 37 C.F.R. §1.111 filed on January 2, 2002 (Paper No. 6). Applicants respectfully request, therefore, that the Examiner withdraw this objection.

REJECTION OF CLAIMS 3, 9, 15, 21, 27, 32, 39, 44, 53, AND 58 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 3, 9, 15, 21, 27, 32, 39, 44, 53, and 58 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. According to the Examiner, this rejection is based on 37 C.F.R. §1.118(a), which states that, "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application." The matter to which the Examiner is referring is the reference to SEQ ID NO:1 in the rejected claims.

Applicants respectfully traverse the Examiner's rejection, but in order to expedite prosecution Applicants have amended the specification to delete reference to SEQ ID NO:1. Moreover, claims 3, 9, 15, 21, 27, 32, 39, 44, 53, and 58 have been cancelled. New claims 69-92 do not include a reference to SEQ ID NO:1. Applicants respectfully request, therefore, that this rejection be withdrawn.

REJECTION OF CLAIMS 1 THROUGH 68 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 1-68 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected to make and or use the invention. According to the Examiner "only the described murine mutant GP IIIa gene, where at least one of the two cytoplasmic tyrosine residues (747 and 759) has been replaced with a phenylalanine residue, meet the written description provision of 35 U.S.C. §112."

The Applicants respectfully traverse the Examiner's rejection. However, in order to expedite prosecution of the present application, Applicants have cancelled claims 1-68 and added new claims 69-92. New claims 69-92 are directed to transgenic **mice**, methods of preparing transgenic **mice**, and methods of using transgenic **mice** wherein the transgenic mice include a mutant GP IIIa (β_3) gene wherein the mutant gene encodes a GP IIIa (β_3) protein having a cytoplasmic domain tyrosine residue replaced with a non-phosphorylatable residue. Thus, the claims as amended now include, with one exception, the combination of limitations which the Examiner has stated meet the written description provision of 35 U.S.C. §112. The one exception is that independent claims 69, 72, 76, 79, 83, 87, and 92 do not include the limitation that the tyrosine residue is replaced with a phenylalanine residue. Such a limitation is not required to render these claims in compliance with the written description provision of 35 U.S.C. §112.

The present invention is directed transgenic mice which have been engineered to express a GP IIIa protein which has one or more of its cytoplasmic domain tyrosine residues replaced with a residue which is non-phosphorylatable. To produce the transgenic mice of the invention, it is only required that one of these tyrosine sites of phosphorylation be replaced with a residue

which is non-phosphorylatable. As those of skill in the art knew, long before the present application was filed, that there are essentially three residues (i.e., serine, threonine, and tyrosine), that are phosphorylatable and that the remainder of the amino acids are not phosphorylatable, there is no requirement that Applicants list each of the non-phosphorylatable amino acids in the present application. Therefore, as Applicants have submitted a claim set which includes claims containing all but one of the limitations required by the Examiner and the one limitation not included in the new claim set is one that is not required to meet the written description provision of 35 U.S.C. §112, the Examiner is respectfully requested to withdraw this rejection.

REJECTION OF CLAIMS 1 THROUGH 68 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 1-68 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains or with which it is most nearly connected, to make and/or use the invention. The Examiner argues that the phenotype of the non-human mammals is not disclosed in the specification and that Exhibit A, submitted in Paper No. 6, relates to mice that "do not contain the same transgene and promoter of the instant invention."

Applicants respectfully traverse this rejection. First, Applicants have cancelled claims 1-68 and added new claims 69-92 that are directed to transgenic **mice**, methods of preparing transgenic **mice**, and methods of using transgenic **mice**. Second, as Applicants stated in their January 2, 2002 Amendment and Reply under 37 C.F.R. §1.111, that the present application does disclose the phenotype of the transgenic mouse. In particular, at page 18, lines 15-18, of the present application, Applicants teach that

> [s]ince the non-tyrosine substitutions will not be phosphorylated as in the case where the residues are tyrosine and since normal platelet aggregation is dependent on phosphorylation occurring, the transgenic mammals of the present invention will display non-normal platelet aggregation.

Moreover, when Applicants cited that Law et al. reference (Exhibit A in Applicants' January 2, 2002 Amendment and Reply under 37 C.F.R. §1.111) to the Examiner, it was to confirm that the transgenic mice of the invention have the very phenotype taught in the present application-that is, non-normal platelet aggregation. The Law et al. reference is a publication by some of the Applicants which describes the production of the SAME transgenic mice of the present invention. In fact, Law et al. describe these transgenic mice as having defective platelet aggregation and clot retraction responses *in vitro* and an *in vivo* bleeding defect (see e.g., page 808, top of the right hand column of Law et al.), thereby confirming the phenotype taught by Applicants in the present application.

The Examiner appears to be confused on one issue with regard to this point. This is evident in the Examiner's statement that the mice of Law et al. contain an αIIbβ3 transgene which is not the same transgene as that of the present invention. This is not correct. Rather, the name "αIIbβ3" is an alternative name for "GP IIb/IIIa" and the GP IIIa gene is also known as the β3 gene (see, e.g., page 1, lines 14-15, page 4, line 6, and page 16, line 8, of the present application).

Therefore, as Applicants have clearly taught a phenotype for the claimed transgenic mice and provided a post filing reference confirming this phenotype, Applicants respectfully request withdrawal of this rejection.

The Examiner also agues that undue experimentation is necessary for the production and methods of use of any non-human mammal and methods of making a non-human mammal expressing a transgene stably introduced into its DNA. Applicants disagree with the Examiner's

argument but in order to expedite prosecution have cancelled previously pending claims 1-68 and have added new claims 69-92 that limit the invention to transgenic mice, methods of preparing transgenic mice, and methods of using transgenic mice. Therefore, Applicants respectfully request withdrawal of this rejection.

REJECTION OF CLAIMS 27, 30, 32, AND 51 UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 27, 30 and 32 are rejected under 35 U.S.C. § 112, second paragraph for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. As Applicants have cancelled claims 27, 30 and 32 and new claims 69-92 do not include the language to which the Examiner objects, Applicants respectfully request that this rejection be withdrawn.

Claim 51 is rejected 35 U.S.C. § 112, second paragraph, because, according to the Examiner, it is unclear how comparing one or more biological responses between a transgenic and non-transgenic non human mammal of the same species relates to determining mutant GPIIIa protein modulation. Applicants have cancelled claim 51 and claims 52-56 and new claims 69-92 do not include a claim or claims which correspond(s) to these cancelled claims. Therefore, the Examiner should withdraw this rejection.

The Examiner also states that it is unclear what "biological" response is being compared in claim 51. New claim 92 does include the term "biological" response. Biological responses are described at page 12, lines 23-30, and at page 13, lines 1-2. In view of this description, Applicants respectfully request that the Examiner withdraw this rejection.

CONCLUSION

The foregoing amendments and remarks are being made to place the Application in condition for allowance. Applicants respectfully request reconsideration and the timely allowance of the pending claims.

This paper is being filed timely as a request for a three month extension of time is filed concurrently herewith. No additional extensions of time are required. In the event any additional extensions of time are necessary, the undersigned hereby authorizes the requisite fees to be charged to Deposit Account No. 501668.

Entry of the remarks made herein is respectfully requested.

Respectfully submitted,

January 27, 2003

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EXHIBIT 1: MARKED UP VERSION OF THE CHANGES TO THE SPECIFICATION

IN THE SPECIFICATION

At page 1, please replace the title with --Transgenic [Mammals] Mice Expressing Mutant GP IIIA (β3) Protein--

At page 19 of the specification, please replace the paragraph at lines 24-31 with the following paragraph:

The sequence for the murine genomic DNA is not known and has not been published, however part of the amino acid sequence of mouse GP IIIa was available (Cieutat et al. (1993) *Biochem et Biophys Res Comm.* 193:771-778, and Dr. Jean-Phillipe Rosa, *Unite INSERM* 348, Paris) and its similarity to human GP IIIa sequence suggested the genomic GP IIIa from humans and mice could be fairly similar. Therefore, several PCR primers were generated towards the mouse GP IIIa sequence in areas which, in the case of human GP IIIa, [(SEQ ID NO. 1] spanned the two exons known to encode the cytoplasmic domain of GP IIIa i.e. Exons M and N (Lanza, F. et al. (1990) *J. Biol. Chem.* 265: 18098-18103). These primers were then tested with total